



Review Article

Imaging and choosing the right patients for transoral endoscopic parathyroidectomy vestibular approach



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Abstract Advances in imaging for preoperative localization have propelled the widespread adoption of minimally invasive/focused parathyroidectomy in primary hyperparathyroidism. Though it is performed through a relatively small incision, studies have shown that the presence of a neck scar increases attentional bias towards the neck resulting in compromised quality of life. Transoral endoscopic parathyroidectomy vestibular approach (TOEPVA) eliminates a neck scar. While indications for TOEPVA are the same as that of minimally invasive open parathyroidectomy, confident preoperative localization of the parathyroid with a surgeon performed ultrasound along with concordant localization with SPECT CT is an essential prerequisite before offering patients this approach for parathyroidectomy. Early data has demonstrated the feasibility and safety of this approach.

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1. Introduction

Once the diagnosis of primary hyperparathyroidism (PHPT) is established, surgical removal of the enlarged gland/s is the definitive management. Bilateral neck exploration (BNE) has been the standard approach to parathyroidectomy. Four gland exploration potentially exposes both the recurrent laryngeal nerves to injury as well as devascularizing normal parathyroid glands which can lead to post-operative hypoparathyroidism. This prolongs recovery and increases the cost of care. Single gland adenoma accounts for more than 80% of primary hyperparathyroidism. With improvements in imaging to localize parathyroid glands and increased use of intra-operative adjuncts, minimally invasive/focused parathyroidectomy (MIP) has gained popularity over the last two decades.¹ Despite a small incision and overall excellent long-term outcome, data has shown that there is a definite discrepancy in perception of the scars between surgeons and patients irrespective of the scar length.² Other studies have demonstrated that the presence of a cervical incision affects the Health-Related Quality of Life (HRQOL) significantly^{3,4} and drives some patients to consider scar revision years after the initial surgery.^{5,6} Attentional bias towards the neck instead of the face and eyes during a conversation due to the presence of a scar after open thyroid/parathyroid surgery has been objectively demonstrated in a recent study by our group.⁷ In addition to impairing cosmesis, the presence of a cervical incision impairs the patient's ability to maintain healthcare privacy. Various remote access approaches to the thyroid have been proposed to obviate a scar. The transoral endoscopic thyroidectomy vestibular approach (TOETVA) popularized by Anuwong has gained acceptance as it is safe and has a short learning curve.⁸ He also proposed the transoral endoscopic parathyroidectomy vestibular approach (TOEPVA), which is materially similar to TOETVA.⁹

2. Indications for TOEPVA

The indications for TOEPVA are the same as those for parathyroidectomy proposed by The Fourth International Workshop in 2014- National Institutes of Health recommendations on the management of asymptomatic PHPT and endorsed by the American Association for Endocrine Surgeons (AAES) are listed in Table 1.^{10,11} Additionally, in our practice, candidates for TOEPVA should be motivated to avoid a cervical incision and also have a well localized adenoma on preoperative imaging. This includes some combination of two separate imaging studies, for example, surgeon directed ultrasound and multi-phase CT.

3. Imaging modalities for localizing the parathyroid gland

The diagnosis of primary hyperparathyroidism is based on biochemical evidence of an elevated serum calcium and PTH level. Imaging for localization should be performed once a decision to pursue surgery is made to guide the approach if TOEPVA is being considered. As above,

Table 1 The indications for TOEPVA.

| |
|---|
| Serum calcium >1 mg/dl (0.25 mmol/L) above the upper limit of the normal level. |
| Creatinine clearance <60 ml/min/1.73 m ² |
| Age <50 y |
| Bone mineral density measurement is reduced >2.5 SD at spine, hip, or radius, or presence of vertebral fracture |
| 24-h urine for calcium >400 mg/d (10 mmol/d) and increased stone risk by biochemical stone risk analysis |
| Presence of nephrolithiasis or nephrocalcinosis |
| Patient requests surgery, or patient is unsuitable for long-term surveillance |

confident and concordant preoperative localization is the sine qua non for focused parathyroidectomy via TOEPVA. The established imaging modalities used for localization of the parathyroid glands are:

- 1) Ultrasound of the neck
- 2) Nuclear medicine: MIBI scan/SPECT
- 3) 2phase CT scan/Multiphase CT scan/4D -CT scan

Less commonly employed in North America are:

- 4) MRI
- 5) PET CT
- 6) Invasive imaging modalities

3.1. Ultrasound

Ultrasound is the first line of imaging that is employed and helps determine if the transoral approach can be offered. It is performed with an ultrasound equipped with a 12–15 MHz linear probe. The specificity of finding a single adenoma is over 90% despite a variable sensitivity of 27%–95% due to the operator dependence.¹² Enlarged parathyroid glands are seen as oval, well circumscribed hypoechoic structures that are distinct from the thyroid gland (Fig. 1). It is our belief that surgeon directed ultrasound is the preferred technique. The ultrasound image not only helps in localizing the gland, it also provides the surgeon information on situation of the gland in relation to fixed anatomic structures. Retrotracheal/retroesophageal parathyroid glands may not be readily visualized and hence may not be ideal candidates for the transoral approach. Ultrasound helps screen the thyroid gland for suspicious nodules which may alter the surgical management or even require further interrogation before surgery. For example, a large thyroid nodule as well a patient who is morbidly obese may reduce the accuracy of localization of a parathyroid adenoma. In addition to performing a surgeon directed ultrasound in the clinic, the authors also prefer intraoperative ultrasound once anesthesia has been induced and the patient has been positioned. This adds to the confidence in identifying the culprit gland precisely in the operative field and to achieve removal with limited dissection and mobilization of the thyroid gland. It is imperative that a surgeon embarking on using this remote



Fig. 1 Right inferior parathyroid gland visualized on surgeon performed ultrasound.

access approach be facile with the use the ultrasound. Surgeon directed ultrasound is a dynamic imaging modality as it gives a real time feedback and allows the surgeon to efficiently formulate a plan for surgery and choose their surgical approach wisely the instant feedback that can be gained from intraoperative ultrasound is invaluable. In our practice, non-localization of the gland on a surgeon directed ultrasound effectively excludes the patient from being offered the transoral approach. The limitations of ultrasound see [Table 2](#).

3.2. Nuclear medicine: MIBI scan/SPECT

The basis for this imaging modality is the high uptake of the radiotracer (Technetium 99 radioisotope) by the mitochondria in parathyroid cells of the adenoma along with the relatively delayed washout. The scan is performed 15 min after the administration of the dye and another scan 2 h later. The sensitivity is about 70% with a positive predictive value of 78%–100%.¹³ False negatives can occur due to predominance of chief cells in the adenoma or a more than rapid washout in the oxyphil cells.¹⁴ Single photon emission computerized tomography (SPECT) with Tc-99m Sestamibi helps to increase the accuracy of localization.¹⁵ The accuracy of nuclear imaging is diminished in the setting of a multinodular goiter or an intrathyroidal adenoma. Non visualization of the gland on nuclear imaging does not preclude open surgery. However, the option of offering TOEPVA to the patient should be

reconsidered unless another imaging modality is concordant with the surgeon directed ultrasound. At our institution, we use customized 2 phase CT that is combined with the nuclear imaging which has been described previously.¹⁶ This not only helps localize the gland with a lower radiation dose but also provides us the anatomical detail and helps is differentiating the superior from the inferior gland that vastly aids in surgical planning.¹⁵ All the scans at our institution are read by a dedicated radiologist who assigns confidence levels ranging from 1 to 3; 1 being the most confident localization read.

3.3. Multiphase CT scan/4D -CT scan

Multiphase CT uses 3 phases (Precontrast, arterial and venous) along with the 4th phase, which is the change in the perfusion over time. The anatomical detail that the multiphase CT provides is excellent and with a sensitivity that is as high as 85%, it may help to identify glands that are missed with the ultrasound or the MIBI scans. It has the additional advantage of detecting multigland disease.^{17,18} There is a small increase in the dose of external radiation that is associated with this imaging modality.¹⁶

3.4. MRI

Magnetic resonance imaging has been used at some centers and has a reported sensitivity of 43%–82%^{19,20} However, it is unsuitable for routine anatomical localization due to high costs and compliance issues. Use of 4D MRI had been recently proposed with a sensitivity of over 80% when performed with dynamic contrast enhancement.^{21,22} We do not routinely utilize this technique.

3.5. PET CT

All the imaging modalities discussed thus far provide anatomical localization but do not indicate the functional status of the parathyroid gland. PET CT using 18F- fluorocholeline is an exception, and has been evaluated for localization with the added advantage of gauging the functional status of the gland. The authors claim that this may help differentiate an adenoma from a hyperplastic gland. Improved spatial resolution and the shortened image acquisition times are additional advantages over the MIBI-CT. The sensitivity is 93.7% with an overall accuracy of 95%.^{23–25}

4. Invasive modalities for localization

Fine needle aspiration cytology along with a PTH washout of the sample under ultrasound/CT guidance had been used to confirm parathyroid tissue in the re-operative setting when imaging reads are not conclusive. PTH levels in the aspirate are more specific than cytology as follicular tissue from the thyroid may be incorrectly identified as parathyroid tissue. We strongly discourage the use of fine needle aspiration in the primary setting as it causes undue scarring making surgery difficult and increasing the risk of nerve injury.

Table 2 Limitations of ultrasound.

| |
|--|
| Skill of the operator |
| Small gland size |
| Concurrent thyroid nodules and pathology. |
| Location of the gland: retroesophageal, mediastinal location |
| Obesity |

Interventional radiology directed localization modalities have also been used. Selective cannulation of the inferior thyroid artery and angiography looking for a vascular blush make it a sensitive modality for localization (25%–70%).²⁶ The risk of embolization and the need for skilled personnel has made the use of this modality extremely rare.

Selective venous sampling uses the gradient in the systemic PTH level compared PTH levels in the superior, middle and inferior thyroid veins or the vertebral/thymic vein and uses it for localization. It needs a skilled operator who can selectively cannulate the veins.

If these techniques are being utilized for parathyroid localization, the patient is likely not an ideal candidate for TOEPVA.

5. Choosing the right patient

The considerations for MIP apply to TOEPVA as well. As with MIP, confident localization of the culprit parathyroid gland is the most important prerequisite to proceed with this approach. Surgeon directed ultrasound of the neck with its high specificity and ability for the surgeon to learn over time is the preferred foundation for TOEPVA in our practice. It helps to effectively exclude patients who may not be candidates for this approach.

Our approach for all patients with primary hyperparathyroidism is to obtain two non-invasive imaging modalities (surgeon guided US and 2 phase MIBI-CT or, if the patient has a MIBI from an outside hospital prior to seeing the authors, that may suffice if it is concordant with the surgeon directed ultrasound). This approach is based on the assumption that when two imaging modalities are concordant, the positive predictive value in localizing the culprit gland is as high as 99%.²⁷ It is our practice to offer TOEPVA only to patients who have positive concordant localization on a surgeon directed ultrasound and a MIBI-CT or MIBI at this time, although we do expect that these indications will expand as our experience increases (Fig. 2).

6. Contraindications to TOEPVA

Inability to localize the enlarged parathyroid gland or discordant results on imaging studies is an important contraindication for TOEPVA. Table 3 summarizes the other contraindications for TOEPVA.

7. Role of intraoperative adjuncts

Intraoperative parathyroid hormone monitoring (IOPTH) has been used in focused parathyroidectomy to predict biochemical cure with a high degree of confidence.¹¹ IOPTH takes advantage of the predictable kinetics of the parathyroid hormone, with a half-life of 1.5–4 min. A pre-incision level is obtained in the preoperative area before administration of anesthetic agents. Then, levels are obtained at 0, 5, 10, 20 and 60 min (in the recovery room) post excision of the culprit parathyroid gland. We have traditionally used the dual criteria (Miami criteria along with fall of PTH into the normal range) in focused open

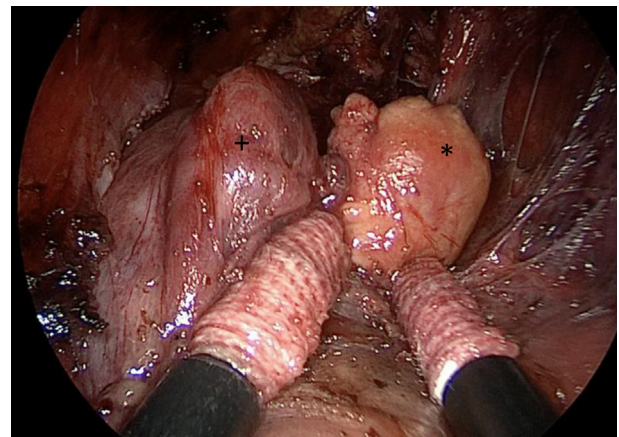


Fig. 2 Intraoperative picture right inferior of the parathyroid gland. (+: Right thyroid lobe; *: Right inferior parathyroid gland).

parathyroidectomy.^{28–30} Data has shown that a 50% drop in the PTH level at 10 min post excision and PTH decreasing to the normal range predict biochemical cure in 97% of patients.²⁸ Additionally, the slope of the PTH values can be valuable. All patients undergoing TOEPVA are counselled about the chance of biochemical failure and the need for an open exploration at a later time or at the same time. This helps to set patient expectations about the chance of failure of the remote access approach, although it is our preference to offer curative surgery at the initial encounter, with conversion for further exploration as needed. Intraoperative exploration can safely be pursued endoscopically if the surgeon understands that an open exploration will follow immediately if the endoscopic exploration is negative.

8. Complications

Experience with TOEPVA is extremely limited, with few reported case series across the world. The complication profile of TOEPVA is similar to TOETVA to date. Only one case of a temporary recurrent laryngeal nerve palsy has been reported thus far in an international case series.⁹ No permanent RLN injury has been reported to date.

Table 3 Contraindications for TOEPVA.

| Absolute contraindications: | Relative contraindications: |
|--|---|
| <ul style="list-style-type: none"> • Equivocal localization studies • Unfit for general anesthesia • Suspected multigland disease | <ul style="list-style-type: none"> • Previous neck surgery • Anticoagulation • Documented contralateral RLN injury |
| <ul style="list-style-type: none"> • Past medical history of head and neck irradiation • Family history of MEN syndrome • Suspected parathyroid carcinoma | |

9. Outcomes

The biochemical cure rates with TOEPVA have been encouraging so far in carefully selected patients. International case series indicate biochemical cure rates between 95% and 100%.^{9,31,32} We recently reported our experience in which the biochemical cure was 100% with no recurrent or mental nerve palsies after performing 21 parathyroidectomies through this approach.³³ The criteria used for biochemical cure and follow up varies widely between institutions and this may make evaluation of future results more challenging.

There are certain factors that may need to be considered before a surgeon embarks on offering the procedure. A high volume endocrine surgeon is best suited to adopt this in his/her practice.³⁴ The experience in treating parathyroid pathology and patient selection will ensure rates of persistent disease are reduced. Rates of primary hyperparathyroidism vary widely across the world; hence it may be difficult to gain experience in a population with low incidence of the disease. Familiarity with laparoscopic instrumentation and technology reduces the learning curve.

10. Conclusion

TOEPVA is a safe and effective approach in the surgical treatment of primary hyperparathyroidism in carefully selected patients. At present, it can be safely offered to patients with a single well localized parathyroid gland, utilizing surgeon directed ultrasound as the initial localization study of choice. With improved experience, it is likely that indications will expand in the future.

Declaration of Competing Interest

Ralph P Tufano – Consultant for Hemostatix and Medtronic. None of the other authors have anything to disclose.

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